Exhibit B

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Analgesic Efficacy and Safety of Oxycodone in Combination With Naloxone as Prolonged Release Tablets in Patients With Moderate to Severe Chronic Pain

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Abstract: This randomized, double-blind, placebo- and active-controlled, parallel-group study was designed to demonstrate the superiority of oxycodone in combination with naloxone in a prolonged release (PR) formulation over placebo with respect to analgesic efficacy. The active control group was included for sensitivity and safety analyses, and furthermore to compare the analgesic efficacy and bowel function of oxycodone PR/naloxone PR with oxycodone PR alone. The analgesic efficacy was measured as the time from the initial dose of study medication to multiple pain events (ie, inadequate analgesia) in patients with moderate to severe chronic low back pain. The full analysis population consisted of 463 patients. The times to recurrent pain events were significantly longer in the oxycodone PR/naloxone PR group compared with placebo ($P < .0001$–$.0003$); oxycodone PR/naloxone PR reduced the risk of pain events by 42% ($P < .0001$; full analysis population). The appearance of pain events was comparable for oxycodone PR/naloxone PR versus oxycodone PR, confirming that the addition of naloxone PR to oxycodone PR in a combination tablet did not negatively affect analgesic efficacy of the opioid. Furthermore, oxycodone PR/naloxone PR offers benefits in terms of an improvement in bowel function. In a therapeutic area of great unmet need, therefore, the combination tablet of oxycodone PR/naloxone PR offers patients effective analgesia while improving opioid-induced bowel dysfunction. Taken together with the observation that the safety profile of oxycodone PR/naloxone PR is consistent with that expected from other opioid analgesics except opioid-induced constipation, these findings indicate that the addition of naloxone to oxycodone in a PR combination tablet offers improved tolerability. Oxycodone PR/naloxone PR is therefore a promising new treatment approach for the management of chronic pain.

Perspective: *This study evaluated the analgesic efficacy and safety of the combination of oxycodone PR/naloxone PR in chronic nonmalignant pain. Opioids are often reduced in dosage or even discontinued as a result of impaired bowel function, leading to insufficient pain treatment. Not only does oxycodone PR/naloxone PR demonstrate analgesic efficacy comparable with oxycodone PR, but it also improves opioid-induced bowel dysfunction, and may therefore improve the acceptability of long-term opioid treatment for chronic pain.*

Key words: Oxycodone, naloxone, prolonged release, chronic pain, bowel function.

Oxycodone is a semisynthetic, strong opioid analgesic,[7] the use of which is well established for the treatment of severe pain.[15] It is effective in cancer-related pain,[7,22] as well as postoperative and osteoarthritis-related pain and neuropathic nonmalignant pain,[15] such as diabetic neuropathy[11,27] and postherpetic neuralgia.[26] Consequently, in recent years, oxy-

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codone has become one of the most highly prescribed opioid for chronic, nonmalignant pain, particularly in patients with osteoarthritic and chronic lower back pain.[7]

Naloxone is a commercially available competitive opioid antagonist, which is intravenously administrated for the blockade of exogenously administered opioids both centrally and peripherally.[5] After oral administration, naloxone has a very low bioavailability of about 2%,[17] owing to an extensive first-pass hepatic metabolism.[5] Therefore, naloxone's systemic availability is negligible; it acts almost exclusively on local opioid receptors in the gastrointestinal tract before undergoing hepatic degradation.[5,10]

The side effects associated with opioid use are well defined and include nausea, sedation, euphoria/dysphoria, constipation, and itching.[2] Although most opioid-related side effects subside with chronic opioid use, constipation persists[2] and is therefore the most frequently reported adverse event in patients receiving opioid treatment.[8] Furthermore, constipation is also often accompanied by other symptoms of bowel dysfunction, such as bloating, abdominal cramping, distension, and increased gastric reflux.[23] This opioid-induced bowel dysfunction occurs regardless of how frequently opioids are used and persists with increasing duration of treatment.[3]

A recent survey of 723 individuals with opioid-induced constipation revealed the high burden of constipation and associated symptoms in terms of patients' quality of life (QoL); both the patients' physical and emotional functioning were limited.[9] Furthermore, opioid-induced constipation increases healthcare resource use and decreases patients' work productivity.[1] Although constipation is well recognised as a common and persistent side effect of opioids, the significance of the impact of opioid-induced constipation symptoms on patient health-related QoL is generally under-recognised by healthcare professionals.[9]

Current management strategies for opioid-induced bowel dysfunction are nonspecific and often ineffective.[17] Prophylactic laxative use improves symptoms in some patients; however, as laxatives do not address the opioid receptor-mediated mechanism of bowel dysfunction, a substantial number of patients do not achieve adequate relief of symptoms.[16,23] Not only does poor management of bowel dysfunction have a negative impact on the patient's QoL,[19] but, in many cases, gastrointestinal side effects may cause patients to reduce or even discontinue their opioid therapy,[16] thereby resulting in analgesic undertreatment. Successful management of pain with opioids therefore requires that the benefits of analgesia outweigh the impact of treatment-related side effects; the achievement of this remains a clinical challenge.[4]

Prevention of opioid-induced constipation, and bowel dysfunction in general, is considered to be a more effective therapeutic strategy than merely treating it when it occurs.[16] The adverse effects of opioids on gastrointestinal function are thought to result primarily from the interaction between opioids and their receptors in the gut.[13,16] It should therefore be possible to block the effects of opioids on bowel function through the administration of an opioid antagonist with selective activity in the gut.[24] Coadministration of oxycodone with an oral opioid antagonist, such as naloxone, is therefore expected to confer advantages with regard to some of the side effects of the drug, particularly constipation. Accordingly, the oral coadministration of oxycodone prolonged release (PR) and naloxone PR has been shown to provide effective analgesia for patients with severe chronic pain, and significantly reduce the impact of opioid-induced bowel dysfunction. The observed improvement in bowel dysfunction was dose-dependent.[21]

Animal studies indicate that the bioavailability of naloxone administered intranasally is much higher than when administered orally, possibly approaching similar bioavailability to intravenous administration.[14] Intranasal administration of naloxone has also been shown to be effective for the reversal of opioid overdose.[18] Taken together, this suggests that abuse of oxycodone PR/naloxone PR by this route would not be attractive.

The current clinical development programme of oxycodone PR/naloxone PR in a combination tablet formulation aims to establish both its analgesic effect (comparison with placebo and with oxycodone prolonged-release) and its effect on bowel function. This Phase III study was conducted to evaluate the analgesic efficacy of oxycodone PR/naloxone PR (ratio of 2:1) compared with both oxycodone PR and placebo over 12 weeks. The evaluation of the effect of treatment on bowel function was an exploratory efficacy measure investigated in a subset of 59 patients with a high bowel function index (BFI) at baseline (ie, those who were constipated).

Materials and Methods

This study was a randomized, double-blind, placebo- and active-controlled, double-dummy, parallel-group study designed to determine the safety and efficacy of oxycodone PR/naloxone PR in patients with moderate to severe, chronic nonmalignant low back pain. The study was conducted in accordance with the Declaration of Helsinki (1964) and all of its accepted amendments to date (Edinburgh, 2000, and Washington, 2002), as well as complying with the principles of Good Clinical Practice (GCP) set by the International Conference on Harmonization and applicable German regulatory requirements. Written informed consent was obtained from patients at screening.

Study Objectives

The primary objective of the study was to demonstrate the analgesic superiority of oxycodone PR/naloxone PR over placebo measured as the time from the initial dose of study medication to recurrent pain events (inadequate analgesia) during the double-blind phase.

Secondary objectives of the study included: To assess the average daily pain during treatment based on the Pain Intensity Scale Average Pain over 24 hours; to compare sleep quality during treatment with oxycodone PR/

naloxone PR versus placebo, and oxycodone PR versus placebo, as measured by the sleep interference item of the modified Brief Pain Inventory Short Form (modified BPI-SF); to compare the total amount of rescue medication (oxycodone immediate release [OxyIR]) used per day (24 hours) in patients receiving oxycodone PR/naloxone PR, oxycodone PR and placebo (OxyIR supplemental dosing).

Exploratory objectives included to assess pain and interference of pain with activities during treatment with oxycodone PR/naloxone PR compared with oxycodone PR and placebo based on the modified BPI-SF and the determination of constipation during treatment with oxycodone PR/naloxone PR compared with that seen during treatment with oxycodone PR. Constipation was assessed using patient bowel function measures (stool frequency, stool consistency, laxative intake) and the bowel function index (BFI; NAS 0–100; mean of the parameters of difficulty of bowel movement, feeling of incomplete bowel evacuation, judgement of constipation).

Patient Population

Males and females at least 18 years of age were enrolled into the study if they had a documented history of moderate to severe chronic nonmalignant lower back pain (eg, osteoarthrosis/osteoarthritis of spine, deforming spondylosis, spondylolisthesis, disc herniation/sciatica, spinal stenosis) adequately managed by an opioid analgesic for at least 2 weeks before study enrolment, and if they received daily opioid analgesic treatment and were likely to benefit from chronic opioid therapy for the duration of the study. Exclusion criteria included: Any history of hypersensitivity to oxycodone, naloxone or related products; patients currently taking the equivalent of <10 mg or >40 mg/d oxycodone; patients diagnosed with cancer (not including basal cell carcinoma); active alcohol or drug abuse; abnormal liver function tests; and patients with a history of >2 lower back surgeries. Patients were also excluded if they had evidence of clinically significant cardiovascular, renal, hepatic, gastrointestinal (paralytic ileus), or psychiatric disease that would have placed the subject at risk upon exposure to the study medication or that could confound the analysis and/or interpretation of the study results.

Study Design

This study was composed of 3 phases: A prerandomization phase; a double-blind phase; and an extension phase. The prerandomization phase comprised 2 periods: The screening period (prospective assessment and opioid taper) and the run-in period (opioid titration). The former involved gradual opioid medication tapering; this down-titration was established to confirm the need for an opioid pain treatment. The latter phase, on the other hand, involved up-titration of OxyIR to achieve adequate analgesia and a stable and comparable pain status for all randomized patients. The double-blind phase was designed to assess the safety and efficacy of oxycodone PR/naloxone PR compared with placebo as a treatment for moderate to severe chronic nonmalignant low back pain. For those patients completing the double-blinded phase, the optional extension phase was designed to assess the long-term efficacy and safety of oxycodone PR/naloxone PR for up to 12 additional months (data presented in a separate publication). The study design is shown in Fig 1.

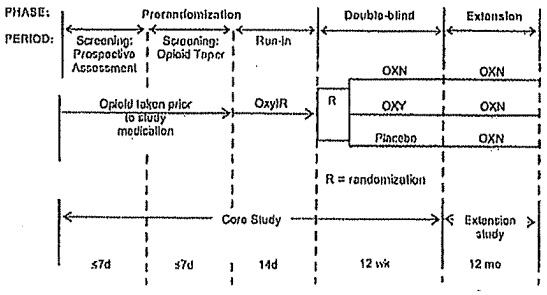

Figure 1. Study design. OXY, oxycodone PR; OXN, oxycodone PR/naloxone PR; OxyIR, oxycodone immediate release.

Treatments

During the screening period (opioid taper), patients could receive OxyIR (OxyNorm; Napp Pharmaceuticals, Cambridge, UK) every 4 to 6 hours when necessary as rescue medication at a quarter of the dose of their previous total daily opioid medication. During the run-in period (opioid titration), the OxyIR dose was titrated to effect; the target dose was 20 or 40 mg/d. At the start of the double-blind phase, all randomized patients were converted from OxyIR to an equivalent study medication dose. Patients randomized to the oxycodone PR/naloxone PR treatment group received a dose of 10/5 mg or 20/10 mg of oxycodone PR/naloxone PR every 12 hours. Patients randomized to the oxycodone PR treatment group received 10 mg or 20 mg oxycodone PR every 12 hours. Patients randomized to the placebo group received matched placebo every 12 hours. Dosing was fixed and equivalent to the effective OxyIR dose identified during the run-in period (opioid titration). During the double-blind phase, all patients could also receive OxyIR every 4 to 6 hours as required as rescue medication at a quarter of the dose of their total daily opioid medication. Patients were instructed to take a dose of OxyIR only when their Pain Intensity Scale ("Pain Right Now") score was ≥5.

Efficacy Assessments

The primary efficacy variable was the time from the initial dose of study medication to recurring pain events during the double-blind phase. A pain event was described as inadequate pain control for 2 consecutive days. A day of inadequate pain control was defined as a Pain Intensity Scale (NAS 0–10; "Average Pain over 24 hours") score ≥5 or a Pain Intensity Scale (NAS 0–10; "Pain Right Now") score ≥5 accompanied by rescue med-

ication dosing ≥2 times over 1 day. The Pain Intensity Scale[6] assessed patients' pain on an 11-point ordinal scale; patients retrospectively assessed their average pain over the past 24 hours each evening ("Average Pain over 24 hours"), as well as assessing their pain at the time immediately prior to rescue medication dosing ("Pain Right Now"). Alternatively, patients were recorded as having a pain event if they discontinued from the study owing to lack of therapeutic effect.

The secondary efficacy variables included the assessment of average daily pain during treatment based on the Pain Intensity Scale "Average Pain over 24 Hours," as well as the interference of pain with the sleep item of the modified BPI-SF, and OxyIR supplemental dosing (rescue medication use) recorded by all patients in their paper diaries.

One of the exploratory efficacy variables was the modified BPI-SF pain subscore. Several exploratory bowel function variables were also assessed. Of these, only BFI, Complete Spontaneous Bowel Movements (CSBM) and percentage of days with laxative intake in the subgroup of patients with BFI values of ≥50 at baseline are reported in this paper. The BFI score of each patient was defined as the mean score of 3 distinct bowel dysfunction components: Difficulty of bowel movement (0–100; 0 = easy/no difficulty, 100 = severe difficulty); feeling of incomplete bowel evacuation (0–100; 0 = not at all, 100 = very strong); and judgment of constipation (0–100; 0 = not at all, 100 = very strong). Higher scores therefore indicate poor bowel function. Assessments were made at five study visits: V4, V5, V6, V7, and V8. A CSBM was defined as a bowel movement without laxative intake in the previous 24 hours (spontaneous) and a feeling of completeness of the bowel evacuation (complete). Assessments were made at baseline and the end of the double-blind phase. In a subgroup of subjects with a BFI value of ≥50 (ie, constipated) at randomization, the percentage of days with laxative intake was also assessed.

Safety Assessments

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, screening subject diaries and monitoring hematology, blood chemistry, urine values, vital signs, ECGs, and physical examinations.

Safety assessment also included evaluation using the modified Subjective Opiate Withdrawal Scale (SOWS). The SOWS consists of 16 items that reflect the common motor, autonomic, gastrointestinal, musculoskeletal, and psychic symptoms of opioid withdrawal.[12] The modified SOWS excluded the SOWS item number 16, "I feel like shooting up today," since it did not apply to the target patient population. Patients were instructed to rate each symptom on a scale of 0 to 4 (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely) based on how they were feeling at the time of answering the questionnaire. Opioid withdrawal was defined as a modified SOWS score >26.

Study Population

The full analysis study population included all patients who were randomized, who received at least 1 dose of study medication and who had at least 1 efficacy assessment in the double-blind phase. The primary efficacy analysis was performed on a total of 463 patients (the full analysis population). The per protocol (PP) population included only those patients who were deemed to have sufficiently complied with the protocol.

Statistical Analysis

The primary efficacy variable (ie, time to recurrent pain events) was evaluated by a time-to-event analysis using the approach of Wei et al,[28] implemented using the Proc PHREG procedure in SAS Version 9 (SAS Institute, Inc., Cary, NC); this used a marginal Cox proportional hazards regression to analyse potentially censored times to repeated events of inadequate analgesia. Using recurrent events in the analysis allowed a fuller use of pain-event information throughout the duration of the clinical trial than would have been allowed from an analysis of the first event only. The regression model included terms for treatment, country, pain during the screening phase and pain during the run-in phase.

The following secondary efficacy variables were analysed using a repeated measures analysis with the mixed effect linear model: Average pain over the last 24 hours; modified BPI-SF interference of pain with sleep item; and OxyIR supplemental dosing. Similarly, for the exploratory variables BFI and BPI-SF pain subscore, a repeated-measures analysis was carried out which included terms for treatment, time as a categorical variable, screening BFI and BPI subscale, respectively, at the end of opioid taper, run-in BFI and BPI subscale, respectively, at the end of opioid titration and country. Laxative intake and CSBMs were analysed descriptively. Moreover for the CSBMs an analysis using a logistic regression was also carried out. The 95% confidence intervals (CIs) for the difference between oxycodone PR/naloxone PR and oxycodone PR (as well as between oxycodone PR/naloxone PR and placebo and between oxycodone PR and placebo) were calculated.

For the safety analyses, all continuous variables were summarized using the following descriptive statistics: n, mean, standard deviation, minimum, median, and maximum. The frequency and percentage of observed levels was reported for all categorical measures. Adverse events were classified by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. All adverse events were listed, summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each system organ class and having each individual adverse event. In addition, the respective absolute number of adverse events was given. Serious adverse events, adverse events leading to death, adverse events leading to discontinuation of study medication, and drug-related adverse events were also tabulated by system organ class

and by preferred term. Treatment-emergent adverse events were summarized by treatment group. Gastrointestinal adverse events were summarized by treatment group, and the mean duration of the adverse event "diarrhea" was displayed.

The sum score of the modified SOWS was calculated by multiplying the mean of the single scores by 15 to adjust the sum score for missing values for each time point of measurement. The sum score was analyzed by a repeated measures analysis that included terms for treatment, time as a categorical variable, screening SOWS sum score, run-in SOWS sum score and country. The 95% CIs for the difference between oxycodone PR/naloxone PR and oxycodone PR (as well as between oxycodone PR/naloxone PR and placebo and between oxycodone PR and placebo) were calculated.

Results

A total of 751 patients were enrolled into the study: Six hundred seventy-six patients entered the opioid taper phase; of these, 73 patients discontinued during this phase. The primary reason for discontinuation was the experience of adverse events (24 patients; 3.6%). A total of 139 patients discontinued during the run-in period (opioid titration); the primary reason for discontinuation during this phase was lack of therapeutic effect (68 patients; 11.3%). A total of 464 patients were therefore randomized into the double-blind phase of the study, and the full analysis population included 463 of these patients. Patient disposition is shown in Fig 2.

All treatment groups were generally well balanced with respect to demographic and baseline characteristics

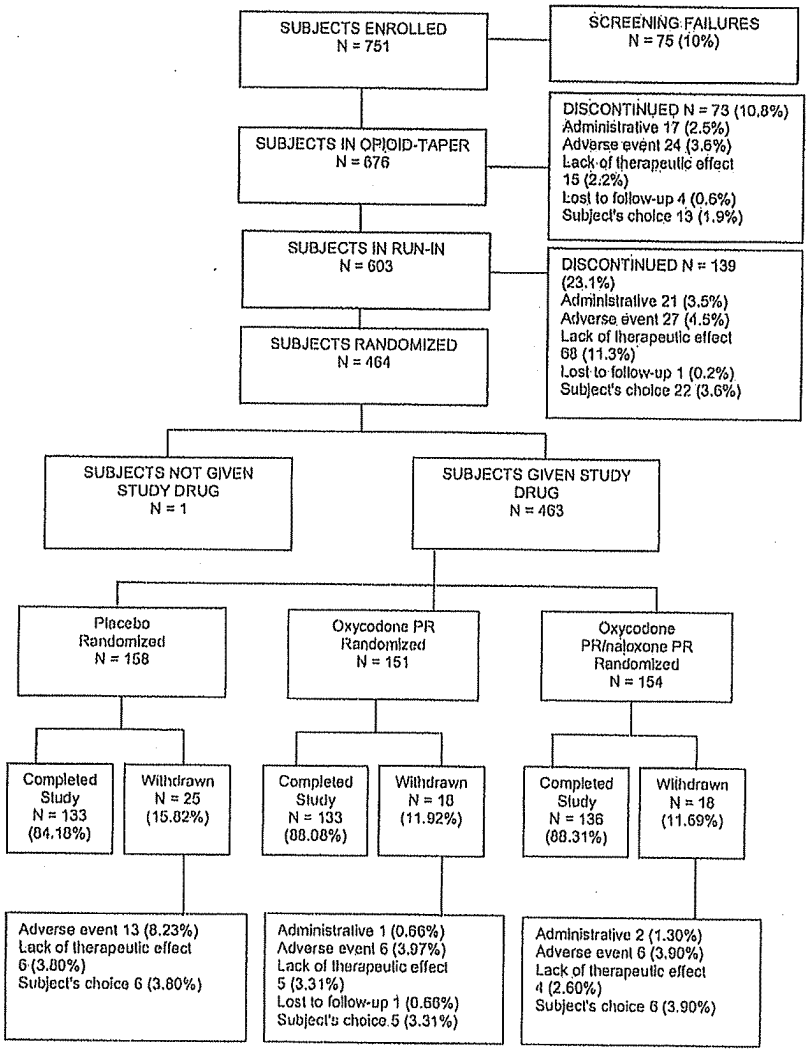

Figure 2. Subject disposition. PR, prolonged release.

Table 1. Patient Demographics and Baseline Characteristics

	Placebo (N = 158)	Oxycodone PR (N = 151)	Oxycodone PR/Naloxone PR (N = 154)	Total (N = 463)
Sex, n (%)				
Male	46 (29.11%)	61 (40.40%)	71 (46.10%)	178 (38.44%)
Female	112 (70.89%)	90 (59.60%)	83 (53.90%)	285 (61.56%)
Age (y)				
Mean ± SD	56.73 ± 11.92	56.47 ± 10.14	55.77 ± 10.81	56.32 ± 10.98
Weight (kg)				
Mean ± SD	80.92 ± 16.92	82.12 ± 17.61	84.41 ± 19.45	82.47 ± 18.04

Abbreviation: PR, prolonged release.

(Table 1). The distribution of males and females was comparable between the oxycodone PR (4:6) and oxycodone PR/naloxone PR groups (4.6:5.4) but slightly different in the placebo group (3:7). This difference occurred randomly and had no influence on the 24 hour average pain or the incidence of adverse events. All patients in the full analysis population suffered from chronic, nonmalignant low back pain and had been previously treated with an opioid analgesic. A high percentage of randomized patients (80.3%) had a low BFI value at baseline (<50) indicating only mild constipation or even the absence of constipation in these patients. No relevant differences were observed between treatment groups for race, mean age and mean weight. Furthermore, there were no clinically relevant differences between the treatment groups with respect to analgesic baseline characteristics, mean daily OxyIR dose, modified BPI-SF interference of pain with sleep item, bowel function characteristics or modified SOWS.

Efficacy Evaluation

The primary objective of the study was to demonstrate the superiority of oxycodone PR/naloxone PR over placebo on the time from the initial dose of study medication to multiple (ie, recurring) pain events (inadequate analgesia) during the double-blind phase. Pain events in the oxycodone PR/naloxone PR group occurred 12 to 15 days later than in the placebo group. The times to pain event were statistically significantly shorter in the placebo group compared with the oxycodone PR/naloxone PR group (P values between < .0001 and .0003). The mean time to first pain event was 19.3 days in the placebo group and 32.2 days in the oxycodone PR/naloxone PR group. Time to recurrent pain events over mean number of pain events by treatment group for the full-analysis population is shown in Fig 3. No statistically significant differences were detected between the oxycodone PR/naloxone PR and the oxycodone PR group.

For the full analysis population, oxycodone PR/naloxone PR was effective in reducing the risk of pain events, with an overall risk of 58% compared with placebo. This relative risk reduction of 42% was statistically significant (hazard ratio [HR], 0.58; CI, 0.46–0.74; $P < .0001$). The risk of experiencing a pain event was 6% higher with oxycodone PR/naloxone PR treatment compared with treatment with oxycodone PR in the full analysis population. However, this result was not statistically significant (HR, 1.06; CI, 0.81–1.39; $P = .6907$). For the per protocol population, oxycodone PR/naloxone PR was also effective in reducing the risk of pain events, with an overall risk similar to the full analysis population (58% compared with placebo). This result was statistically significant ($P = .0014$). Furthermore, the risk of experiencing a pain event was 13% lower with oxycodone PR/naloxone PR treatment compared with oxycodone PR treatment in the per protocol population; however, as in the full analysis population, this result was not statistically significant ($P = .4497$). Overall, these results demonstrate a significantly rarer appearance of pain events under oxycodone PR/naloxone PR compared with placebo and a comparable incidence of pain events for oxycodone PR/naloxone PR versus oxycodone PR.

Throughout the double-blind phase, patients in the oxycodone PR/naloxone PR ($P = .0396$) and the oxycodone PR ($P = .0080$) treatment groups showed statistically significantly lower "Average pain over the last 24 hours" scores compared with placebo. Subjects in the placebo group had significantly higher BPI-SF pain subscores compared with subjects in the oxycodone PR group ($P = .0012$) and oxycodone PR/naloxone PR group ($P = .0158$). Similarly, there was a significant improvement in the interference with sleep score of the BPI-SF scores in both the oxycodone PR ($P = .0030$) and oxy-

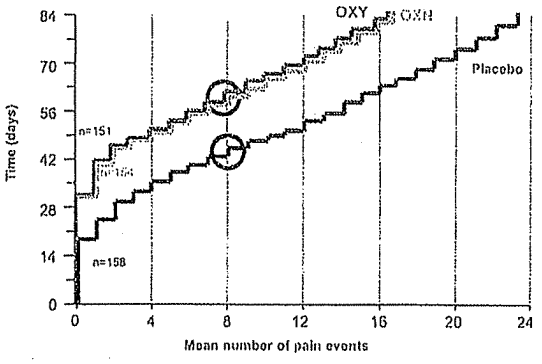

Figure 3. Time to recurrent pain events over mean number of pain events by treatment group: Full analysis population. OXY, oxycodone prolonged release (PR); OXN, oxycodone PR/naloxone PR.

codone PR/naloxone PR ($P = .0057$) groups compared with placebo, and the intake of rescue medication was also significantly higher in the placebo group than both the oxycodone PR ($P < .0001$) and oxycodone PR/naloxone PR ($P = .0004$) groups. In a subgroup analysis of the "Average pain over the last 24 hours" scores during the double-blind phase, in patients with a BFI of ≥50 at baseline, pain values increased in the oxycodone PR group (3.70–4.50) and in the placebo group (3.59–4.58), whereas they remained stable in the oxycodone PR/naloxone PR group. In the last treatment period (days 57–84), pain values were about 10% lower in patients receiving oxycodone PR/naloxone PR compared with those receiving either oxycodone PR or placebo.

Table 2. BFI Scores and CSBMs: Subgroup Population (Subjects With BFI ≥ 50 at Visit 4)

	Oxycodone PR (N = 30)	*Oxycodone PR/Naloxone PR (N = 29)*
BFI score		
Visit 4 (baseline)		
n	30	29
Mean ± SD	63.9 ± 10.1	65.7 ± 13.6
Visit 5 (week 2 of double-blind phase)		
n	28	25
Mean ± SD	46.9 ± 24.7	45.7 ± 30.0
Visit 6 (week 4 of double-blind phase)		
n	28	25
Mean ± SD	45.0 ± 25.7	44.8 ± 30.1
Visit 7 (week 8 of double-blind phase)		
n	26	25
Mean ± SD	48.1 ± 21.8	43.5 ± 30.1
Visit 8 (week 12 of double-blind phase)		
n	28	28
Mean ± SD	52.6 ± 25.2	42.6 ± 27.5
CSBM		
Baseline*		
n	30	29
Mean ± SD	2.40 ± 1.90	1.93 ± 2.20
End of double-blind Phase*		
n	26	25
Mean ± SD	2.08 ± 2.46	4.20 ± 3.18
CSBM1†		
Nonresponders	23 (76.7)	11 (37.9)
Responders	7 (23.3)	18 (62.1)
CSBM3‡		
Nonresponders	20 (66.7)	11 (37.9)
Responders	10 (33.3)	18 (62.1)

Abbreviations: BFI, bowel function index; CSBMs, complete spontaneous bowel movements; PR, prolonged release.

*Number of complete spontaneous bowel movements (CSBMs) during the last 7 days before visit 4/visit 8.

†CSBM1 responders: Subjects who had at least 1 more CSBM in the week before end of DB phase compared with the week before baseline.

‡CSBM3 responders: Subjects who had at least 3 CSBMs in the week before end of DB phase.

In the subgroup of patients that had a BFI value ≥50 at visit 4 (ie, those who were moderately or severely constipated; Table 2), a medically relevant difference in BFI score decrease was observed between the oxycodone PR/naloxone PR group and the oxycodone PR group. The BFI scores decreased between visit 4 and visit 8 by 23.1 in the oxycodone PR/naloxone PR group and by 11.3 in the oxycodone PR group. No statistical analysis was done on this subgroup of patients owing to an insufficient number of subjects. The mean number of CSBMs also increased strongly (ie, improved) in this patient subgroup; an increase of 2.27/week (1.93–4.20) was seen with oxycodone PR/naloxone PR, whereas a decrease (ie, worsened) by 0.32/week (2.40–2.08) was seen with oxycodone PR. The percentage of CSBM1 responders (patients who had an increase of at least 1 CSBM in the week before the end of the double-blind phase compared with the week before baseline) was higher in the oxycodone PR/naloxone PR group (62.1%) compared with the oxycodone PR group (23.3%). Furthermore, the percentage of CSBM3 responders (patients who had at least 3 CSBMs in the week before the end of the double-blind phase) was also higher in the oxycodone PR/naloxone PR group (62.1%) compared with the oxycodone PR group (33.3%). The results of the BFI scores and number of CSBMs therefore indicate that there is a clinically relevant improvement in bowel function with oxycodone PR/naloxone treatment PR compared with oxycodone PR treatment.

Laxative use was assessed in the subgroup of subjects with BFI values ≥50 at visit 4. In these patients, laxative intake (mean percentage of days with laxative use) decreased over the course of the double-blind phase in the oxycodone PR/naloxone PR group (18.4%–15.6%), and increased in the oxycodone PR group (13.7%–24.3%). Laxative use in the full analysis population was also lower in the oxycodone PR/naloxone PR group compared with that reported for the oxycodone PR group; patients had a mean of 7.85% of days with laxative intake in the oxycodone PR/naloxone PR group and 10.36% of days with laxative intake in the oxycodone PR group.

Safety Evaluation

The primary safety analyses were performed on all patients who received study drug during the double-blind phase and had at least 1 postdose safety assessment during this phase of the study (double-blind safety population). A total of 463 patients were included in this analysis.

Overall, the incidence of adverse events during the double-blind phase was comparable between the different treatment groups (placebo: 52.5%, oxycodone PR: 53.0%, and oxycodone PR/naloxone PR: 55.8%). The incidence of adverse events is shown in Table 3. Constipation (8.4%), nausea (7.1%), headache (4.8%), vomiting (4.3%), and diarrhea (4.1%) were the most frequently reported treatment-emergent adverse events. The incidence of constipation was highest in the oxycodone PR

Table 3. Incidence of Adverse Events: Double-Blind Safety Population (≥5% of Patients)

	Placebo (N = 158)	*Oxycodone PR (N = 151)*	*Oxycodone PR/Naloxone PR (N = 154)*	*Total (N = 463)*
System organ class/preferred term	n (%)	n (%)	n (%)	N (%)
Overall incidence of adverse events	83 (52.5)	80 (53.0)	86 (55.8)	249 (53.8)
Gastrointestinal disorders				
Constipation	8 (5.1)	18 (11.9)	13 (8.4)	39 (8.4)
Diarrhea	7 (4.4)	4 (2.6)	8 (5.2)	19 (4.1)
Nausea	11 (7.0)	12 (7.9)	10 (6.5)	33 (7.1)
Vomiting	5 (3.2)	7 (4.6)	8 (5.2)	20 (4.3)
General disorders and administration site conditions				
Fatigue	4 (2.5)	8 (5.3)	4 (2.6)	16 (3.5)
Nervous system disorders				
Dizziness	6 (3.8)	9 (6.0)	2 (1.3)	17 (3.7)
Headache	11 (7.0)	6 (4.0)	5 (3.2)	22 (4.8)

Abbreviation: PR, prolonged release.

group (11.9%) followed by the oxycodone PR/naloxone PR (8.4%) and the placebo (5.1%) groups. The incidence of nausea was comparable between the different treatment groups (oxycodone PR 7.9%, placebo 7.0% and oxycodone PR/naloxone PR 6.5%), and the incidence of headache was higher in the placebo group (7.0%) compared with the other treatment groups (4.0% and 3.2% in the oxycodone PR and oxycodone PR/naloxone PR, respectively). The incidence of diarrhea was slightly higher in the oxycodone PR/naloxone PR and placebo groups (5.2% and 4.4%, respectively) than in the oxycodone PR group (2.6%). The percentage of patients with gastrointestinal adverse events was comparable across all treatment groups, with slightly higher numbers in the oxycodone PR group (27.2% compared with 23.4% [placebo] and 22.7% [oxycodone PR/naloxone PR]). Most adverse events were mild or moderate in intensity and the incidence of severe adverse events was low.

The incidence of adverse events leading to discontinuation during the double-blind phase was very low. The adverse events which most frequently led to discontinuation were nausea (n = 8), vertigo/dizziness (n = 5), vomiting and hypertension (n = 4, each). The percentage of patients with related serious adverse events (SAE; according to the investigator) was generally very low. A slightly higher incidence of SAEs was observed in the oxycodone PR/naloxone PR group (2.6%) compared with the oxycodone PR (0.0%) and placebo (0.6%) groups. In the oxycodone PR/naloxone PR group, only 4 patients experienced SAEs that were possibly related to the study drug. There were no treatment-related deaths during the course of the study.

The adverse events, SOWS sum scores, clinical laboratory, vital sign and ECG results of potential clinical concern were reviewed. No apparent safety concerns of treatment with oxycodone PR/naloxone PR were identified.

Discussion

Discussion of Efficacy

The results of this study clearly demonstrate the analgesic superiority of oxycodone PR/naloxone PR combination tablets over placebo, as well as revealing that the addition of naloxone PR to oxycodone PR does not negatively affect analgesic efficacy of oxycodone PR. The times to pain events were significantly shorter in the placebo group compared with the oxycodone PR/naloxone PR group (P values between $< .0001$ and $.0003$). For both the full analysis and per-protocol populations, the appearance of pain events was significantly rarer under oxycodone PR/naloxone PR compared with placebo; combination therapy reduced the risk of pain events to 58% ($P < .0001$ and $P = .0014$, respectively).

These data are supported by the observation that, throughout the double-blind phase, patients in the oxycodone PR/naloxone PR group showed statistically significant lower 24-hour average pain values ($P = .0396$), BPI-SF pain subscores ($P = .0158$), frequency of OxyIR intake ($P = .0004$) and BPI-SF sleep interference scores ($P = .0030$) compared with the placebo group. The appearance of pain events was comparable for oxycodone PR/naloxone PR versus oxycodone PR, as were the effects of treatment on 24-hour average pain values, BPI-SF pain subscores, OxyIR intake and BPI-SF sleep interference scores, confirming again that the addition of naloxone PR to oxycodone PR did not negatively affect analgesic efficacy. The recurrent pain event analysis used in the study assumed that the pain events occur independently. Zeng and Lin[29] have developed a method to overcome this restriction; however, this method is relatively new and not implemented in SAS Version 9.1.3 (SAS Institute, Inc.). It therefore was only used as a supportive analysis, and the results of this supportive analysis confirmed that the findings of this study are reproduced if the method of Zeng and Lin is used, thereby lending further support to the study findings and their validity.

The results of the BFI scores and number of CSBMs showed a clinically relevant improvement in bowel function with oxycodone PR/naloxone PR treatment compared with oxycodone PR treatment in the subgroup of patients with BFI values ≥50 at Visit 4. BFI scores declined in patients receiving oxycodone PR/naloxone PR but remained stable in patients receiving oxycodone PR. The percentage of patients who were CSBM1 and CSBM3 responders was higher in the oxycodone PR/naloxone PR group compared with the oxycodone PR group. Furthermore, for the subgroup of patients with BFI ≥50 the mean percentage of days with laxative use decreased over the course of the double-blind phase in the oxycodone PR/naloxone PR group, whereas an increase was observed in the oxycodone PR group. These results are further supported by the findings of other bowel function measurements, including the percentage of days with at least 1 complete bowel movement, the percentage of days with at least 1 nonhard bowel movement and the mean stool frequency (data not reported here).

The observation that the coadministration of oxycodone PR/naloxone PR significantly improves bowel function, as well as providing effective analgesia in patients with severe chronic pain, supports the findings of an earlier study by Müller-Lissner et al.[21]

Discussion of Safety

The safety profiles of oxycodone and naloxone are well established. The overall incidence of treatment-emergent adverse events was comparable between the different treatment groups. Across all treatment groups, the following were the most frequently reported treatment-emergent adverse events; constipation (8.4%), nausea (7.1%), headache (4.8%), vomiting (4.3%), and diarrhea (4.1%). The majority of adverse events were mild or moderate in intensity and are consistent with the expected adverse event profile of opioid analgesics. Importantly, adverse events and SOWS sum scores were not exacerbated by the addition of naloxone PR to oxycodone PR therapy. Furthermore, owing to the low number of patients that experienced SAEs possibly related to treatment, oxycodone PR/naloxone PR showed no additional risk compared with oxycodone PR treatment.

Owing to the local action of the naloxone component of oxycodone PR/naloxone PR on the gastrointestinal tract, gastrointestinal adverse events were of particular interest. The total number of patients with gastrointestinal adverse events was comparable across all treatment groups, with slightly higher numbers in the oxycodone PR treatment arm. The incidence of constipation (as ascertained through adverse event reporting) was highest in the oxycodone PR group (11.9%) followed by the oxycodone PR/naloxone PR (8.4%) and the placebo (5.1%) group. Constipation was not defined medically in this investigation, but the incidence was ascertained through the use of AE reporting. The number of patients experiencing diarrhea was generally low in all treatment groups. The incidence of diarrhea in the oxycodone PR/naloxone PR group (5.2%) was comparable with the placebo group (4.4%) and therefore not regarded as being related to study drug. The mean duration of diarrhea was generally short and was shorter in the oxycodone PR/naloxone PR group (3.57 days) compared with the other treatment groups (4.71 days placebo group, 5.25 days oxycodone PR group). Analysis of adverse events, SOWS sum scores and standard safety tests revealed no clinically relevant safety concerns related to treatment with oxycodone PR/naloxone PR. Throughout the double-blind phase mean SOWS scores were stable, low, and comparable in all treatment groups, indicating that the addition of naloxone PR to oxycodone PR does not lead to withdrawal or compromised analgesic efficacy. A total of 8 patients (3 patients receiving placebo, 1 subject receiving oxycodone PR and 4 subjects receiving oxycodone PR/naloxone PR) showed opioid withdrawal defined as SOWS sum scores >26 during the double-blind phase. Only one of these patients (placebo group) had elevated SOWS sum scores throughout the study. This was probably owing to the lack of regular opioid intake by this patient (OxyIR was only permitted as rescue medication), and therefore this adverse event was not deemed to be medically important.

Overall 10 patients experienced 24 SAEs during the course of the study. This high number of SAEs was mostly due to the reporting strategy (SAEs were defined as all signs and symptoms reported by the investigator and each individual sign and symptom was regarded as an SAE). On evaluation, only 4 patients in the oxycodone PR/naloxone PR group had an SAE that was deemed to be possibly related to treatment.

Discussion of Study Design and Chosen Treatments

The design of the study allowed the patients to take OxyIR as rescue medication, thereby mimicking the usual practice of prescribing a dose of immediate-release opioid as needed for pain. The study assessed maintenance of analgesia with repeated-events analysis. Direct measures of pain over a 12-week period were needed to demonstrate long-term efficacy of oxycodone PR/naloxone PR versus placebo. As described in the Materials and Methods, a composite measure of pain event was used for the primary end point and was based on 3 pain criteria: Pain intensity scale; rescue medication dosing ≥2 times over a single day; or study discontinuation owing to lack of therapeutic effect. At the same time, therefore, this design avoided the issue of rescue use potentially confounding pain measurements since pain measurement at the time of rescue intake was incorporated into the definition of the primary efficacy variable. Discontinuation owing to lack of efficacy was also included in the efficacy analysis as it was deemed to indicate inadequate pain control.

In the limited available studies exploring the impact of naloxone immediate release (IR) on opioid-induced constipation, naloxone IR has been associated with opioid withdrawal symptoms, even at low doses.[17,20,24] Furthermore, in some patients, naloxone IR has been associated with a reversal of analgesia or the necessity to increase

the opioid dose given.[17] In the current study, naloxone PR was used. It is hypothesised that the slow release of naloxone may reduce the risk of systemic antagonism by relieving the burden placed on the hepatic enzymatic systems responsible for its metabolism. The results of a previous study show that the use of naloxone PR does indeed reduce the risk of systemic antagonism and the coadministration of naloxone does not therefore reduce the analgesic efficacy of the opioid.[21] These findings are confirmed in the current study.

The dose ratio of oxycodone PR/naloxone PR used in this study (ie, 2:1) was chosen based on evidence from a previous study in which the overall improvement in bowel dysfunction at a dose ratio of 2:1 was approximately 50% higher than that seen at a dose ratio of 4:1 ($P < .05$) and the 1:5:1 dose ratio was associated with high efficacy, but was not as well tolerated as the 2:1 ratio.[21] The oxycodone PR comparator was chosen for sensitivity and safety analyses. In the primary analysis, the comparison between oxycodone PR and placebo was made to assess sensitivity of the clinical trial and to facilitate the interpretation of the clinical trial in the eventuality of a nonsignificant primary comparison.

The efficacy measurements used in the study are those commonly used to evaluate pain in patients with chronic nonmalignant pain. The BPI-SF has been validated for use in this patient population and its interference subscale was used to provide a QoL measure. This scale has also been validated in several languages, and is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a group convened in the United States to evaluate end points in pain studies.[25]

Randomization was used in this trial to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) were evenly balanced across treatment groups and to enhance the validity of statistical comparisons across treatment groups.

Conclusions

This study provides evidence that oxycodone PR/naloxone PR is superior to placebo, and comparable to oxycodone PR, with regards to analgesic efficacy. At the investigated dose, the addition of naloxone to oxycodone in a prolonged release combination tablet has no negative impact on the analgesic efficacy of opioid treatment, and demonstrates further benefits in terms of an improvement in bowel function. Both the BFI scores and number of CSBMs revealed a clinically relevant improvement in bowel function with oxycodone PR/naloxone PR treatment compared with oxycodone PR treatment in the patients with BFI values of ≥50 at baseline. Furthermore, the percentage of days with laxative use was also less in the oxycodone PR/naloxone PR group compared with the patients that were randomized to receive either placebo or oxycodone PR alone. In an area of great unmet need, therefore, the combination tablet of oxycodone PR/naloxone PR offers patients effective analgesia while improving opioid-induced bowel dysfunction. Taken together with the observation that the safety profile of oxycodone PR/naloxone PR is consistent with that expected from other opioid analgesics, these findings indicate that the addition of naloxone to oxycodone in a prolonged release combination tablet may improve the acceptability of opioid treatment in this patient population and may therefore represent a promising new treatment approach for the management of chronic pain. Doses equivalent to oxycodone PR 80 mg/day (and up to 160 mg/d in a subpopulation) have been investigated in other studies and data will be presented elsewhere.

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